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MUTUAL RECOGNITION AGREEMENTS

Between the EU and the respective Parties Australia, Canada, New Zealand and Switzerland

Guide to the MRAs in operation

Status

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MUTUAL RECOGNITION AGREEMENTS
Medicinal Products GMP Inspection and Batch Certification

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I Introduction

This guide is intended to provide an information package for the European Union (EU) on the key elements of the respective Mutual Recognition Agreements in operation. The countries Australia, Canada, New Zealand and Switzerland are referred to as "MRA Partner Countries" in this paper. All other countries outside the European Economic Area (EEA) are referred to as "Third Countries".
Although there are differences between the legal texts of the various MRAs this document attempts to present the common elements.

1. Purpose of the MRAs

The European Community (EC) and MRA Partner Countries have established the MRAs to:

(a) Reduce technical barriers to trade by facilitating market access while safeguarding consumer interests in health,

(b) grant mutual acceptance of reports, certificates, authorisations, conformity marks issued by the regulated authorities of the Parties and the manufacturers' declarations of conformity certifying conformity to the requirements of the other Party,

(c) exchange information concerning procedures used to ensure that the conformity assessment bodies comply with the general principles of designation and

(d) encourage greater international harmonisation.

2. Scope and coverage

The Agreements on Mutual Recognition in Relation to Conformity Assessment between the European Community and the respective MRA Partner Country cover in their specific Annexes medicinal products (see Appendix B - Part 2), which have undergone one or a series of manufacturing processes in the respective MRA Partner Country and/or in the European Union, and to which Good Manufacturing Practice requirements apply in both jurisdictions. This includes manufacturing, labelling, testing and wholesaling activities. It is limited to the manufacturing process(es) carried out and subject to inspections in the respective territories of the MRA Partner Country and the European Union.

According to the specific Annexes – regarding Medicinal Products and Good Manufacturing Practices (GMP) - the premise of the MRAs is that the MRA Partner Country and the EU Member States mutually recognise

- the relevant manufacturing authorisations granted by the competent authorities of the other Party,
- the conclusions of inspections of manufacturers carried out by the relevant inspection services of the other Party,
- the manufacturers' certification of the conformity of each batch to its specifications by the respective Party without re-control at import.

3. Benefits for regulators and industry

An operational mutual recognition agreement (MRA) provides assurance that equivalent GMP standards are applied by the Parties of the MRA and removes the need for additional inspection and re-controls at import:

> Benefits for authorities: According to Article 20 of Directive 2001/83/EC or Article 24 of Directive 2001/83/EC respectively competent authorities shall verify that manufacturers and importers of medicinal products are able to carry out manufacture and/or controls in compliance with the requirements of the marketing authorisation and in accordance with GMP

at least equivalent to the EU. This requirement also applies for manufacturers in third countries. To verify the GMP status of manufacturers the competent authorities perform many overseas inspections. Instead of these inspections, GMP certificates issued by the MRA Partner Countries' authorities can be accepted with an MRA in operation (They are still possible if deemed necessary for public health reasons though). The MRAs help to use resources more economically.

Benefits for industry: Importers in the EU must have a Qualified Person who is responsible to certify that each production batch meets its specification. According to EC legislation all necessary quality control tests have to be repeated in the EU in advance of a certification. The re-control is expensive and causes delays in entering into the market. An operational MRA is considered to be an appropriate arrangement for the Qualified Person to rely on the batch certification of the third country manufacturer if the provisions set out in Annex 16 of the EC GMP guide are fulfilled. However, tests may be conducted if the Qualified Person deems it necessary. These arrangements help industry to save resources and time.

II Contents of the MRAs

1. Scope

"Medicinal Products" - in the context of MRAs - means all products regulated by pharmaceutical legislation of the European Community and/or the respective MRA Partner Country as listed in the MRA. The MRAs may apply to bulk, intermediate and finished products[1].

The definition of medicinal products includes all human and veterinary products, such as chemical and biological pharmaceuticals, immunologicals, radiopharmaceuticals, stable medicinal products derived from human blood or human plasma, pre-mixes for the preparation veterinary medicated feeding-stuff. Investigational medicinal products and medicinal gases are also covered.

The MRAs apply for vitamins, minerals, herbal remedies and homeopathic medicinal products, if these products are classified as medicinal products in the respective legislation.

Example: Some vitamin products are classified as food supplements and others as medicinal products depending on the amount of active ingredient. Only those vitamins classified as medicinal products are covered, vitamins marketed as food supplements are not included in the MRAs.

The difference in scope of the individual MRAs is illustrated in Appendix B.

2. Territorial application

The medicinal product must be industrially manufactured in the EU and/or the MRA Partner Country. Chemical active ingredients and other starting material from third countries may be used. If the product is partially manufactured in a third country the MRA does not apply. Therefore the company has to re-control the batch prior to release for sale in the EU. The inspection of the MRA Partner's authority at this (partially) manufacturing site in their territory shall be recognised.

Example: The granulate is manufactured in the USA and imported into Switzerland. After further manufacturing steps the finished products cannot be imported into the EU without further re-control. A GMP certificate issued by the Swiss authority to the Swiss manufacturing site shall be recognised).

[1] Definitions in Vol. 4 of the Rules governing Medicinal Products in the European Union are applicable.

3. Key Elements

3.1 Certification of GMP compliance of manufacturers

All operational MRAs provide for a GMP compliance certificate to be issued by the local authority.

3.1.1 Purpose of the certificates

The purpose is to certify that the manufacturer (or laboratory)

is appropriately authorised to manufacture the relevant medicinal product, or to carry out the relevant specified manufacturing or testing operation

and (or) is regularly inspected by the authorities

and complies with the national GMP requirements recognised as equivalent by the two Parties.

In the exceptional case different GMP requirements would be used as reference, this is to be mentioned in the certificate.

3.1.2. Request for a certificate

At the request of an exporter, importer or the competent authority of the other Party, the authorities responsible for granting manufacturing authorisations and for supervision of the manufacture of medicinal products will issue certificate of GMP compliance. The certificate will also identify the site of manufacture.

Certificates shall be issued expeditiously, and the time taken should not exceed **thirty** calendar days. In exceptional cases, i.e. when a new inspection has to be carried out, this period may be extended to sixty days.

For the purpose of these agreements, the manufacturing company can request an inspection be made by the local competent inspection service.

3.1.3 Process/product orientated inspections prior marketing authorisation

Sometimes these inspections are also referred to as "pre-authorisation" or "pre-approval" inspections. The MRAs only apply to process/product orientated GMP-inspections performed by the GMP-inspectorates. The evaluation of raw data during the assessment process of a marketing authorisation application is not covered by these agreements.

The format of the GMP certificate is available at the EMEA web site.

3.2 Batch Certification

All operational MRAs provide for a batch certificate to be issued by the manufacturer.

3.2.1. Purpose of the certificate

The purpose of the certificates is to attest that the quality of the product is in accordance with the requirements of the marketing authorisation and that the batch meets these specifications.

Each batch transferred between countries having an MRA in force, must be accompanied by a batch certificate issued by the manufacturer in the exporting country. The importer of the batch has to receive and maintain this batch certificate. Upon request, it has to be readily available to the regulatory authority of the importing country. This manufacturers' certification on the conformity of each batch is essential to exempt the importer from re-control (re-analysis).

This certificate shall be issued further to a full qualitative and quantitative analysis of all active and other relevant constituents to ensure that the quality of the products complies with the requirements of

the marketing authorisation of the importing country. It will attest that the batch meets the specifications and has been manufactured in accordance with the marketing authorisation of the importing country, detailing the specifications of the product, the analytical methods referenced, the analytical results obtained and containing a statement that the batch processing and packaging quality control records were reviewed and found in conformity with GMP. The batch certificate will be signed by the person responsible for releasing the batch for sale or supply/export at the manufacturing site.

Where applicable this batch certificate may also be used for non-finished medicinal products such as bulk, partially packed and intermediate products as well as for active pharmaceutical ingredients.

The content of the batch certificate has been harmonised and agreed by all MRA partners. It is available at the EMEA web site.

3.2.2. Responsibilities of Qualified Persons

In the European Union the person responsible for releasing the batch for sale or supply is referred to in Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC as the "Qualified Person".

The Qualified Person of an importer in the EU (holder of the manufacturing authorisation according to Article 40 of Directive 2001/83/EC or Article 44 of Directive 2001/82/EC respectively) is responsible for ensuring the quality of imported medicinal products in accordance with the requirements of the marketing authorisation and must certify that the batch meets the requirements set out in Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC respectively before it can be released for sale.

According to Paragraph 7.1 of Annex 16 to the EU Guide to GMP the Qualified Person may certify the batch when he/she is satisfied with the manufacturer's confirmation that the batch has been made and tested in accordance with its marketing authorisation, the GMP requirements of the MRA Partner Country, that the batch has been transported under the required conditions, and has been received and stored in the EU by an importer.

He/she may rely on the written confirmation of the manufacturer on the manufacturer's batch certificate, which must accompany each batch imported into the EU, without further testing. In this case the responsibilities should be ensured by a written agreement .

For details see Annex 16 of the EC Guide to Good Manufacturing Practices.

3.3 Specific provisions for products covered by legislation of one Party but not the other

With respect to medicinal products covered by the legislation of one Party but not the other, the manufacturing company can request an inspection to be made by the local competent inspection service for the purpose of this agreement. This provision shall apply inter alia to the manufacture of active pharmaceutical ingredients, intermediate products and investigational medicinal products, as well as to the process/product orientated inspections prior marketing authorisation.

In those cases the locally competent authority should inspect against its own GMP requirements, or in absence of specific requirements, against the applicable GMP requirements of the importing Party.

Nevertheless the MRAs do apply for these products. In addition any amendment to the current legislation may change the status of a group of products.

Example: Investigational medicinal products are going to be covered by EC legislation from 1 May 2004. The certification scheme will apply as described in 3.1 and 3.2.

The EC legislation contains additional requirements for biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, GMP requirements apply for some starting materials of these products. The provisions of 3.1 and 3.2 apply.

"Legislation" in the context of MRAs means the legislation regarding medicinal products as listed in the Annexes of the respective MRA. Legislation not listed is not applicable in the MRA. If products are covered by the legislation of one Party but not regarded as medicinal products in the other Party - though regulated - they shall be treated as "products covered by the legislation of one Party but not the other" (see above).

Example: Instable blood products are regulated by the Directive 2002/98/EC on human blood and blood components. This Directive is not listed in the MRAs. Blood products are covered by the Swiss legislation regarding medicinal products. Therefore the MRA applies in the way described above.

3.4 Alert System

The alert system agreed in the framework of the MRA ensures that batch recalls and other safety measures resulting from quality defects of medicinal products discovered by one Party are transmitted to the MRA Partner without any delay. This is one of the main pillars of the MRAs.

It is based on the current rapid alert system (RAS) operational in the EEA and in the respective MRA Partner Country. The RAS and templates forms are part of the Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections.

The alert system also provides for communication of counterfeiting and fraud. Suspension and withdrawals of manufacturing authorisations shall be communicated through the alert system as well.

In the MRA between the EC –and Canada specific provisions were agreed (see Two-way Alert Procedure, EC-Canada MRA).

3.5 Official batch release

The official batch release procedure is an additional verification of safety and efficacy of immunological medicinal products (vaccines) and blood derivatives, carried out by competent authorities before the distribution of each batch of product.

In general this is not covered by the MRAs (exception see below) and the procedure will be repeated by the authority of the importing Party at importation of the products mentioned above. In addition the importer has to provide this certificate issued by the authority of the exporting Party at request of the importing Party.

III Specific contents

1. Additional coverage and specific provisions for Switzerland (see also Questions & Answers)

In principal there are two procedures for import from the EU into Switzerland and from Switzerland into the EU, respectively:

1.1 Importation into the EU from Switzerland

The importer of the batch has to receive and keep the batch certificate issued by the manufacturer. There should only be one "Official Importer" into the EU per entire batch of medicinal product, and it is the Qualified Person of this importer who bears overall responsibility for the import and subsequent traceability of the batch within the EU and for the retention of the manufacturer's batch certificate.

The Qualified Person of the "Official Importer" takes account of the manufacturer's batch certificate, normally without further re-control, and certifies in a register that the legislative requirements have been satisfied. This "Official Importer" in the context of this MRA fulfils the duties of the "importer of the first part of the batch" as described in Article 6.3.3 of Annex 16 to the EC Guide to Good Manufacturing Practice.

1.2 Importation into Switzerland from the EU

The importer of the batch has to receive and keep the batch certificate issued by the manufacturer. The Responsible Person of the importer bears the responsibility for the import and subsequent traceability of the batch within Switzerland and for the retention of the manufacturer's batch certificate and samples. The Responsible Person of the importer takes account of the manufacturer's batch certificate, normally without further re-control, and keeps records of all batches released by him onto the market.

By doing this, the Responsible Person of the importer assures that each batch or part of a batch meets the legislative requirements before it can be released. It is possible that physical import of parts of a single batch of a product may take place at different times and sites. In the latter case the Responsible Person at either site may release the batch or parts of the batch of a product onto the market.
The responsibilities of the manufacturer and of the importer, the responsibilities of the Qualified Person(s) in the EU and the Swiss Responsible Person(s) will be defined in a formal document (contractual or technical agreement).

1.3 Official batch release

In addition official batch release carried out by an authority of the exporting Party will be recognised by the other Party:
When an official batch release procedure applies, official batch release carried out by an authority of the exporting Party will be recognised by the other Party. The manufacturer shall provide the certificate of the official batch release.

The Swiss and EU Official Medicines Control Laboratories (OMCL) are entitled to exchange the individual analytical results of a batch. Should a batch not be found to comply with the specifications, this information should be provided rapidly using the rapid information OMCL Network System. Switzerland is included and participates in the OMCL Network.

2. Maintenance Programmes

The MRA with Canada provides for Maintenance Programme to ensure that equivalence is maintained in the operational phase. This programme has been implemented in order to continuously monitor the GMP Compliance Programmes of Regulatory Authorities (R. A.) deemed to be equivalent at the conclusion of the confidence building period and any subsequent decisions concerning that equivalence.

The maintenance programme includes the following:

- Evaluating changes that have an impact on the programme delivery;
- Monitoring of the R. A. deemed equivalent;
- Integration of new R. A. in the MRA
- Making recommendation to the Joint Sectoral Group (JSG) for integration/deletion of R. A. in Appendix 2 of the Sectoral Annex of the MRA agreement.
- Providing joint training opportunities
- Resolving problems, which may occur.

The maintenance programme includes annual reporting by the regulatory authorities to the other party.

IV Where to obtain more information

On the web sites of the EMEA (www.emea.eu.int) an overview of the MRA and related topics is available

Contact details of authorities, rapid alert contacts and contacts for requesting GMP certificates can be optained by sending an email to mra@emea.eu.int.

Appendix A List of Regulatory Authorities in Europe and MRA partner countries

Regulatory Authorities in Europe
(Please provide updates to mra@emea.eu.int currrent as of April 2003)

Country	H/V	Contact
Austria	H+V	Bundesministerium für soziale Sicherheit, Generationen und Konsumentenschutz Radetzkystraße 2 A – 1031 Vienna
Belgium	H+V	Directoraat generaal Geneesmiddelen Direction générale Médicaments RAC Vesaliusgebouw Pachecolaan 19 bus 5 B – 1010 Bruxelles
Denmark	H+V	Lægemiddelstyrelsen Frederikssundsvej 378 DK – 2700 Brønshøj
Finland	H+V	Lääkelaitos P.O. Box 55 FIN – 00301 Helsinki
France	H	Agence Française de Sécurité Sanitaire des Produits de Santé 143-147 Boulevard Anatole France F – 93285 Saint-Denis CEDEX
France	V	Agence Française de Sécurité Sanitaire des Aliments La Haute Marche Javané F – 35133 Fougères
Germany	H+V	Bundesministerium für Gesundheit und Soziale Sicherung Am Propsthof 78a D – 53121 Bonn
Germany		**Biologicals**: Paul-Ehrlich-Institut Federal Agency for Sera &Vaccines 63207 Langen
Greece	H+V	National Organisation for Medicines Mesogion 284 155 62 Holargos Athens
Ireland	H+V	Irish Medicines Board The Earlsfort Centre Earlsfort Terrace IRL – 2 Dublin
Italy	H	Ministero della Salute Dipartimento Valutazione Medicinali e Farmacovigilanza Viale della Civiltà Romana, 7 I – 00144 Rome
Italy	V	Ministero della Salute Dipartimento Alimenti e Nutrizione e Sanità Pubblica Veterinaria Ufficio XI Piazzale G Marconi, 25 (Palazzo Italia) I – 00144 Rome
Luxembourg	H+V	Ministère de la Santé Division de la Pharmacie et des Médicaments Villa Louvigny, Allée Marconi L – 2120 Luxembourg

Netherlands	H+V	Staatstoezicht op de volksgezondheid Inspectie voor de Gezondheidszorg PO Box 16119 NL - 2500 Den Haag
Portugal	H+V	Instituto Nacional da Farmácia e do Medicamento Parque de Saudé de Lisboa Av do Brasil 53 P - 1700 Lisboa
Spain	H+V	Agencia española del medicamento C/ Huertas, 75 E - 28014 Madrid
Sweden	H+V	Läkemedelsverket Box 26 S – 751 03 Uppsala
United Kingdom	H+V	Medicines and Healthcare products Regulatory Agency Market Towers 1 Nine Elms Lane UK – London SW8 5NQ
United Kingdom	V	**Veterinary Immunologicals:** Veterinary Medicines Directorate Woodham Lane New Ham, Addlestone Surrey KT15 3NB

Regulatory Authorities in MRA Partner Countries

Australia	H	Therapeutic Goods Administration (TGA) Department of Health and Family Services PO Box 100 Woden ACT 2606
	V	National Registration Authority for Agricultural and Veterinary Chemicals POBox E240 Kingston ACT 2604 Australia
Canada	H	Health Products and Food Branch Inspectorate 1001 St-Laurent West Longueuil, Québec J4K 1C7
New Zealand	H	Ministry of Health Therapeutics Section P.O. Box 5013 Wellington
	V	Ministry of Agriculture Agricultural Compounds and Veterinary Medicines Group PO Box 2835 Wellington
Switzerland	H+V	Swissmedic Schweizerisches Heilmittelinstitut Erlachstrasse 8 CH-3000 Bern 9

H = Human medicinal products
V = Veterinary medicinal products

Appendix B Part 1 – Overview of the MRAs, Pharmaceutical Annex

Element/Country	Australia	Canada	New-Zealand	Switzerland
Status	In force since 1 Jan 99 (H) 1 Jul 01 (V)	In force since 1 Feb 03	In force since 1 Jan 99 (H) 1 Jun 02 (V)	In force since 1 June 02
Agreement published in	OJ L 229, 17/08/1998	OJ L 280, 16/10/1998	OJ L 229, 17/08/1998	OJ L 114, 30/04/2002
Amendments published in	OJ L 278, 16/10/2002	OJ L 278, 16/10/2002	OJ L 278, 16/10/2002	OJ 56, 01/03/2003 OJ 66, 11/03/2003 OJ L68, 12/03/2003
Exchange of inspection report	Upon reasoned request full or detailed inspection report			
Exchange of Certificates of GMP compliance of a manufacturer	• 30 days • 60 days, if new inspection			
Batch certificate	=> Internationally Harmonised Requirements for Batch certification			
Two-way Alert system	Yes			
Joint activities	Yes			

Part 2 - List of products covered by the respective Pharmacutical Annex

Scope and coverage (all products regulated by the Pharmaceutical legislation in the EC and the MRA Partner, see text)	**Australia**	**Canada**	**New-Zealand**	**Switzerland**
Human pharmaceuticals **Non-prescription and prescription**	Yes	Yes	Yes	Yes
Medical gases	Yes	Yes	Yes	Yes
Human biologicals: vaccines, immunologicals and biotherapeutics	Yes	Yes	Yes	Yes
Stable medicinal products derived from human blood or blood plasma	Yes	**No**[#]	Yes	Yes
Veterinary pharmaceuticals: **Non-prescription and Prescription**	Yes	Yes	Yes	Yes
Veterinary premixes and preparations for medicated feed (US: preparation Type A)	Yes	Yes	Yes	Yes
Veterinary immunologicals	Yes	**No**	Yes	Yes
Vitamins minerals* **Herbal remedies**	Yes	Yes	Yes	Yes
Homeopathic medicinal products*	Yes	Yes	Yes	Yes
Product intended to be used in clinical trials, investigational medicinal products[+]	Yes	Yes	Yes	Yes
Intermediate products and bulk pharmaceuticals	Yes	Yes	Yes	Yes
Active pharmaceutical ingredients[+]	Yes	Yes	Yes	Yes
Process/product orientated inspection prior marketing authorisation	Yes	**No**[3]	Yes	Yes
Official batch release	**No**	**No**	**No**	Yes

* Where appropriate, if medicinal products
[+] GMP currently not applicable in both Parties
[#] as agreed during the evaluation period

Appendix C List of References

EC legislation/regulations

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products

Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of Good Manufacturing Practice for medicinal products for human use

Commission Directive 91/412/EEC of 23 June 1991 laying down the principles and guidelines of Good Manufacturing Practice for veterinary medicinal products

The Rules Governing Medicinal Products in the European Union, Volume 4, GMP

Annex 16 of the EC Guide to Good Manufacturing Practice (in operation since January 2002) Certification by a Qualified Person and Batch Release

Notice To Applicants Vol. 2A (Jan 2001) Procedures for marketing authorisation Chapter 4 Centralised Procedure.

Notice To Applicants Vol. 6A (April 2001) Procedures for marketing authorisation Chapter 4 Centralised Procedure

Commission Regulation (EC) No 541/95, as amended, concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State.

Commission Regulation (EC) No 542/95, as amended, concerning the examination of variations to the terms of a marketing authorization falling within the scope of Council Regulation (EEC) No 2309/93

Compilation of Community procedures on administrative collaboration and harmonisation of inspections

Mutual Recognition Agreements of Conformity Assessment, Certificates and Markings between the European Community and the respective MRA Partner Country and agreed documents

Australia

Sectoral Annex: Medicinal Products GMP Inspection and Batch Certification

Canada

Sectoral Annex on Good Manufacturing Practices (GMP)
Two-Way Alert System
Standard Operating Procedure for the Determination of Equivalency of Inspection Methods
Maintenance Programme

New Zealand

Sectoral Annex: Medicinal Products GMP Inspection and Batch Certification

Switzerland

Agreement between the European Community and the Swiss Confederation on mutual recognition in relation to conformity assessment (OJ L 114 of 30 Apr 02), Chapter 15
Explanatory Notes to Chapter 15 (Medicinal Products GMP inspection and batch certification) of Annex 1 of the EU-Swiss MRA
Decision No 2/2002 of 8 January 2003 on the modification of the Annex 1 of the Agreement

[DC1]